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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,798	08/25/2003	Anurag Rathore	161765.00520	3621

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EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/646,798	RATHORE ET AL.	
	Examiner	Art Unit	
	Satyanarayana R. Gudibande	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-76 is/are pending in the application.

4a) Of the above claim(s) 69-76 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-68 is/are rejected.

7)☐ Claim(s) 2-68, 75 and 76 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/14/04 & 4/21/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I invention in the reply filed on October 3, 2005 is acknowledged. The traversal is on the ground(s) that there are two criteria for a proper restriction, a) the inventions must be independent or distinct and b) there must be a serious burden on the Examiner if restrictions required. This is not found persuasive because the applicant's arguments that the inventions are not distinct or independent and does not requires burdensome search to examine the application as a whole is wrong for the following reasons. The fact that use of mercapto compound is forbidden in the presence of a metal salt during purification process clearly and distinctly separates group I and II inventions. Likewise, the use of a chelating agent in the presence of a metal salt during purification procedure as indicated in groups II and III moots the primary reasons behind using these reagents to remove the impurities, because the reagents operate by different modes and have different functions. As for the question of burdensome search involved in looking for prior art in the non-patent literature, researchers do not use ingredients that have opposite effects in the same procedure to prove a point that they cannot be used together. Hence, different searches are required to obtain information from multiple sources examine an application that has multiple inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 69-76 have been withdrawn from consideration as not directed to the elected invention of group I.

Claim Objections

Claims 2-68, 75 and 76 are objected to because of the following informalities: use of the term "embodiment" instead of "claim". Appropriate correction is required.

Objections to Specification

Inclusions of flow charts in the specifications has been objected to in accordance with 37 CFR 1.58(a). Graphical illustrations, diagrammatic views, flowcharts, and diagrams in the descriptive portion of the specification do not come within the purview of 37 CFR 1.58(a), which permits tables, chemical and mathematical formulas in the specification in lieu of formal drawings. Applicants are required to make appropriate correction to specification in accordance with 37 CFR 1.81.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jespersen, et al., Eur. J. Biochem., 1994, 219, 365-373, in view of US patent 5,849,535 issued to Cunningham, and further in view of Houk, et al., J. Am Chem. Soc., 1987, 109, 6825-6836.

In the instant application, applicants claim a process for decreasing trisulfide impurity in recombinant production of a growth hormone antagonist polypeptide in genetically modified host cells. The steps involved in reducing the trisulfide impurity during the process involved contacting the impurity with a mercapto compound, growing the host cells to produce the polypeptide, purifying the polypeptide and pegylating the polypeptide.

Jespersen, et al., teaches the characterization of a trisulfide derivative of human growth hormone produced in E. Coli. The reference uses 1,4-dithiothreitol to reduce the full-length derivative of the growth hormone for electrospray mass spectroscopy (page 367, column 1). Jespersen, et al., also discuss the aspect of trisulfide formation in the E. Coli cells due to the presence of high concentration of H_2S present during cell disruption (Page 372, column 1). The trisulfide bond could be formed by a HS^- attack on a disulfide linkage of the cysteine. The mechanism is reversible and hence the liberation of H_2S was observed with the treatment of cysteine on the growth hormone (page 372, column 2). The reference does not teach the pegylation of the protein and use of functional equivalents of other mercapto reducing agents. The reference does not teach using the method for reducing the trisulfide impurity for antagonist.

Cunningham, et al., discloses a method for the preparation human growth hormone antagonist, B-2036 variants (example V in columns 56-61), that encompass the pegylation of the growth hormone (column 64). The described method meets the limitations of the 10-50 mM tris buffer temperature, pH (column 59), and volume of the buffer used during the process (column 58). However, the method described does not use mercapto compounds as reducing agents.

The reference of Houk, et al., discusses the structure-reactivity relations for number of thiol compounds, which are functional equivalents of the compounds recited the instant application. The list of compounds (on pages 6830 and 6831) can be used individually or in combinations of others for the purpose of reducing the disulfide bonds or trisulfide linkages.

In the present application, applicants have disclosed a process for reducing the trisulfide impurity during the isolation of the growth hormone antagonist from the recombinant method in E. Coli. The process involves the use of mercapto compounds to reduce the trisulfide linkages

and pegylation of the resulting growth hormone. Jespersen, et al., identifies the trisulfide bond in the growth hormone isolated from E. Coli by recombinant techniques. They have shown the use of mercapto compounds to reduce the trisulfide impurity in the preparation. Jespersen, et al., have also shown how the trisulfide bonds break up in the presence of mercapto compounds such as 1,4-dithiothreitol and cysteine. Cunningham, et al., have disclosed the method of preparation of growth hormone variants including B-2036, which is an antagonist. The reference also teaches the pegylation procedure for the growth hormone. Houk, et al., teaches the structure-reactivity relationships of several dithiol compounds that are functional equivalents of the compounds recited in the instant application. The human growth hormone variant with substitution mutation at G120K acts as a hormone growth hormone antagonist. Hence, the method of purification that worked for the growth hormone should work for the antagonist. The B-2036 human growth hormone variant has nine mutations compared to the human growth hormone (column 4, US patent 5,849,535). Therefore, there would have been reasonable expectation of success given the knowledge that presence of mercapto compounds reduces the trisulfide impurity in the growth hormone produced from E. Coli and can be pegylated using the method taught by Cunningham, et al. Therefore, it would be prima-facie obvious to combine the teachings of Jespersen, Cunningham and Houk to develop method for the production of growth hormone antagonist from E. Coli with reduced presence of trisulfide impurity.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

srg

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